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Lana Liem
Director
Regulatory Affairs

August 26, 1999

Docket Management Branch (HFA-305)
Food & Drug Administration
5630 Fishers Lane, room 1061
Rockville, MD 20852

RE: Draft Guidance "Changes to an Approved NDA or ANDA"
Docket No. 99D-0529

Dear Sir or Madam:

Pfizer is hereby submitting comments to the Draft Guidance "Changes to an Approved NDA or ANDA" published June 1999. Although the increased clarity is helpful, we believe that the overall regulatory burden to the industry has not been significantly reduced. The attached tables summarize our comments with suggested improvements. Please contact me with any questions or comments at (212) 573-3833.

Sincerely,

Lana Liem

Lana Liem

99D-0529

C14

Comments on:

Draft FDA Guidance "Changes to an Approved NDA or ANDA" (Docket No. 99D-0529)
Table of Specific Comments
August, 1999

Line Number	Comment	Rationale
101-103	This statement needs to clarify the definition of the applicant's FDA district home office to which copies of supplements are sent. The guidance should clarify whether these documents are sent to the applicant's FDA district office for the location from which the documents are sent or to the FDA district office where the change is being made. If the latter and in the case of site changes, clarify whether copies should be sent to the FDA district offices for both the pre-existing and new alternate sites. If the change affects multiple sites, clarify whether copies should be sent to each affected FDA district office. Also, for international changes, clarify which FDA district office should receive copies.	To ensure that copies of the supplemental applications are received by the appropriate FDA district office(s)
105, 107, 111 and throughout guidance	Suggest changing the word "validate" to "assess" and delete footnote. As suggested in the footnote, this could be confused with CGMP validation. In fact, line 112 uses the word "assessing" in parentheses to show equivalence to "validating".	To avoid confusion with CGMP validation.
155-157	Clarify demonstration of equivalence for drug substance intermediates.	According to the BACPAC I guidance, demonstration of equivalence for drug substance intermediates can be performed at the processing step where the change is

		made or at any subsequent step. This does not require demonstration of equivalence for the drug product.
190	Suggest substitution of the word "appearance" for "color".	Some ingredients, such as the use of a clear overcoat on a film-coated tablet are meant only to enhance the appearance and handling characteristics of the drug product.
213-215	Recommend deletion of point 2 and adding "current" in front of "satisfactory CGMP inspection". Same comment for lines 250-255.	The critical point here is the demonstration of a satisfactory and recent CGMP inspection of the facility for the type of operation involved. There is also lack of definition of what constitutes discontinuation of an operation.
266-267	Delete "modified release solid oral dosage forms" from list of examples.	Most modified release solid oral dosage forms are robust products manufactured with processing technology equivalent to immediate release solid oral dosage forms.
288-291	Delete "or within a single facility (e.g., room changes).	This type of change should be annual reportable. The requirement for a satisfactory CGMP inspection of the facility should already have been met for a change within a single facility.
314-340	Delete items 1, 2, 3, 5, 7 and 8.	These examples of annual reportable changes should be deleted since the original application does not include the baseline data.
333-336	Delete items.	Reporting changes to simple floor plans that do not affect the production process/contamination precautions or improvements to manufacturing areas that provide greater assurance of quality adds no value to the application yet increases regulatory burden.
408	Clarify the meaning of "fundamental change in the manufacturing process or technology".	This phrase is vague and subjective. Need to provide a more definitive explanation of a fundamental change instead of examples.
408-409	Change Section VII.B.4 to apply only to drug product.	This section is confusing since it seems to apply to both

		drug product and drug substance. However the third example of filtration to centrifugation would not be considered a major change for drug substance processing. The process of isolation for a drug substance or drug substance intermediate should be classified as a minor change.
414	Move this example under Section VII.B.5 for changes to a drug substance.	To consolidate drug substance changes, including the route of synthesis of a drug substance, under one category is less confusing.
416	Insert the word "major" to read "Any major process change..."	This statement needs further clarification and perhaps some examples. For instance, changes in scale or equipment of similar design should not be considered major changes as long as the proper assessment of equivalence pre- and post- change is performed. We suggest that this guidance be consistent with BACPAC with regard to categorizing changes.
467	Add "and changes that do not involve new starting materials or intermediates" after "as a starting material".	To be consistent with BACPAC I, changes involving solvents, reagents, process parameters and purification procedures in one or more steps in the synthetic procedure should be categorized as moderate changes.
477-479	Suggest adding an example that allows the addition or tightening of process parameters (or ranges) and/or equipment specifications for both drug product and drug substance manufacturing processes.	Adding or revising process parameters or process parameter ranges with the intent of providing additional information to increase quality assurance should be annual reportable.
530-531	Delete example #3	Provided that the analytical procedure distinguishes impurities within the acceptance criteria described in the application, limit of detection and limit of quantitation are irrelevant.
538-539	Modify this statement to include changes in specifications but to exclude minor revisions.	Minor editorial, non-substantive revisions to specifications or analytical procedures should be annual reportable. Examples of these types of changes are

		formatting and typographical corrections.
551-562	Re-classify these examples as minor changes.	Changes to specifications or methods which provide the same or increased assurance of the identity, strength, quality, purity or potency of the material being tested should be annual reportable.
584-585 794-799	Delete these examples for reference standards.	Since specifications for reference standards are not generally part of the original application, these sections should be deleted.
617-621	Delete this example.	While it is important to assess whether inks/adhesives used for semi-permeable or permeable packaging components to ensure that they do not interact with the product, this is not required to be included in an NDA/ANDA. Filing this as a prior approval supplement is unnecessary provided that assessment is performed through extractable testing. This is not addressed in the draft stability guidance or recently issued packaging guidance.
622-624	Clarify the types of changes which require prior approval supplements. This example is too vague.	Minor changes to primary packaging components should not require prior approval supplements. An example of this would be a minor decorating change to a dosing device, such as a dropper/spoon/cup, which have a low probability of affecting the dose.
638-639	Insert the word "Major" before the phrase "changes in the size...."	Minor cosmetic changes in size and shape of container for sterile drug substance or sterile drug product, which do not impact on seal integrity, protective properties, surface area or headspace, should not be classified as requiring a prior approval supplement.
642	Clarify moderate changes with examples instead of including all changes except as otherwise listed.	This category seems to be a "catch all" category for all changes not listed as major or minor. Many changes that are presently considered to be annual reportable that are not listed would then require CBE's creating an

		increased regulatory burden.
661-662	Delete the words "containing the same number of dose units".	A change in size and/or shape of a container for nonsterile solid dosage forms should also be acceptable as an annual reportable change since bracketing of counts is done routinely to justify a count change.
663	Add words "multiple dose unit" before "container closure system..."	All examples cited are specific to multiple dose unit containers. This should be specified to avoid confusion for this section.
679-682	Add "colorant" to list of changes.	If this example is to include specific types of materials used in the production of the container/closure then colorants should be included. In addition, how would other examples such as new supplier and/or new process with same specification or decreasing wall thickness be categorized?
695-700	Clarify with examples.	Examples for multiple dose containers and nonsterile liquid oral and topical dosage forms are included in the guidance. Examples for unit dose container/closures should also be given to be consistent and to avoid misinterpretation.
711-713	Delete this example.	Changes to secondary packaging components when they are not intended to provide additional protection to the drug product should not be reportable as the information would not have been filed in the NDA/ANDA originally.
781	Delete "or based on pilot scale batch data". Also need to define pilot scale batch size in glossary for all dosage form types.	Extension of expiration dating based on pilot scale batches included in the original application should be achievable via annual report.
793	Revise this sentence to "Addition of test points, storage conditions or analytical procedures to the stability protocol".	Adding additional test points, storage conditions and analytical procedures to the stability protocol should all be annual reportable since all provide increased stability evaluation.

Misc.	Terms such as raw materials and starting materials are not defined in glossary.	A full glossary of terms used in the guidance is critical to avoid any confusion or misinterpretation.

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